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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. |
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| 09/380,422 | 09/01/99 | SAMADPOUR M | MD9501 |

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LEGAL PATENTS
WILMINGTON DE 19898

| EXAMINER | |
|---|---|
| LU,F | |
| ART UNIT | PAPER NUMBER |
| 1655 | 4 |

DATE MAILED: 06/20/01

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

| Office Action Summary | Application No. 09/380,422 | Applicant(s) SAMADPOUR, MANSOUR | |
|---|---|---|---|
| | Examiner Frank W Lu | Art Unit 1655 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

**Attachment(s)**

15)☒ Notice of References Cited (PTO-892)
16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3* .
18)☐ Interview Summary (PTO-413) Paper No(s). _____ .
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other: .

## DETAILED ACTION

### *Location of Application*

1. The Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1655.

### *Priority*

2. An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification (37 CFR 1.78).

### *Drawings*

3. The specification contains brief description of the Figures 1a to 16b. However, no figure can be found in this instant application. Applicant is required to furnish a drawing under 37 CFR 1.81. No new matter may be introduced in the required drawing.

### *Specification*

4. This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

***Claim Rejections - 35 U.S.C. § 112***

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 7, 8, 10 and 17 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for separating DNA fragment from 0.1 to 18 kb using gel electrophoresis selected from the group consisting of 2 dimensional gel electrophoresis, and field inversion electrophoresis, does not reasonably provide enablement for a method for separating small DNA fragments such as 0.1-0.2 kb using pulsed field electrophoresis or a method for separating larger DNA fragment such as 10-18 kb using capillary gel electrophoresis. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Note that claims 8-10 are dependent on claim 7.

In *In re Wands*, 858 F.2d 731,737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) the court considered the issue of enablement in molecular biology. The Court summarized eight factors to be considered in a determination of "undue experimentation". These factors include: (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the relative skill of those in the art; (g) the predictability of the art; and (h) the breadth of the claims. The Court also stated that although the level of skill in molecular biology is high, results of experiments in molecular biology are unpredictable.

To begin, there is no direction or guidance in the specification to show the separation of a digested small DNA fragments such as 0.1-0.2 kb using pulsed field electrophoresis and the separation of digested large DNA fragments such as 10-18 kb using capillary gel electrophoresis. While the relative skill in the art is very high (the Ph.D. degree with laboratory experience), there is no predictability whether digested small DNA fragments from 0.1 to 0.2 kb can be separated by pulsed field electrophoresis or digested large DNA fragments from 10-18 kb can be separated by capillary gel electrophoresis. Note that the specification only provides a working examples (see pages 14-21) to show the separation of digested DNA fragments from 0.1 to 18 kb using regular agarose gel. During prior art search, the examiner could not found a prior art that described the separation of digested DNA fragments from 0.1 to 1 kb using pulsed field electrophoresis or the separation of digested DNA fragments from 10 to 18 kb using capillary gel electrophoresis. It has been know that pulsed field electrophoresis was be used to separate DNA fragments in size from 20 Kb to 10 Mb (see Pharmacia Catalogue, pages 154 and 155, 1996) and capillary gel electrophoresis was be used to separate DNA fragments in size less than 2 kb (Arakawa *et al.*, (J. Chromatography A, 664, 89-98, 1994). Accordingly, it is concluded that undue experimentation is required to make the invention as it is claimed. See M.P.E.P.*§§* 706.03(n) and 706.03(z).

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 16-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Note that claims 17-27 are dependent on claim 16.

9. Claims 16 are rejected as vague and indefinite over the phrase "the lowest index of diversity" or "the highest index of diversity" because it is unclear what it intended. Note that, although the specification define "index of diversity" as the number of discrete subtypes identified by the number of isolates analyzed by a specific subtyping method, the examiner did not understand exact meaning of "index of diversity". For this examination, the examiner considered "index of diversity" as a percent of the particular number identified from the whole number of isolates. Please confirm that this is an accurate interpretation.

10. The term "the lowest index " or "the highest index" in claim 16 is a relative term which renders the claim indefinite. The term "the lowest index" or " the highest index" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

***Claim Rejections - 35 U.S.C. § 102***

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 1-4, 6, 11, 12, 16, 19, 21, 25, and 26 are rejected under 35 U.S.C. 102(b) as being anticipated by Preston *et al.,* (J. Clin. Microbiology, 32, 1427-1430, 1994).

Preston *et al.,* teach genetic variability and molecular typing of *Shigella sonnei* strains isolated in Canada. In this study, restriction fragment length polymorphisms (RFLPs) of genomic DNAs from 49 clinical isolates of *Shigella sonnei* were analyzed by using a modified restriction endonuclease analysis procedure to investigate the genetic variability of this species. After cleavage with the restriction enzyme HaeIII or RsaI (4 base cutters as described in claims 11, 12, 16, and 21), DNA samples were electrophoresed in 5% polyacrylamide gels (16 cm long and considered as about 12 cm as described in claim 25) and the RFLP patterns were visualized by silver staining. The results showed that among 20 strains associated with sporadic cases of infection in three Canadian provinces, 15 distinct RFLP patterns were revealed by HaeIII digestion (the highest index of diversity from the unlinked isolates: 16/20=80%) and 12 distinct patterns were revealed by RsaI digestion (the lowest index of diversity from the unlinked isolates:13/20=65%). In contrast, the RFLP patterns of individual isolates within six groups of epidemiologically related isolates were identical to each other (the lowest index of diversity from the linked isolates are 9.1% (1/11) for RFLP pattern I, 8.3% (1/12) for RFLP pattern II, and 33.3% (1/3) for RFLP pattern III) but distinct from those of unrelated isolates (see abstract in page 1427, right column in column 1428, and Table 1 in page 1429). Note that polyacrylamide gel used by Preston *et al.,*could separated fragment in the 0.1 to 18 kb range as described in claim 1 (see Figure 2 in page 3181) since the range of Hae III digested genomic DNAs on the gel (see

page 1428 and 1429, Figures 1 and 2) were from ~0.1 kb to 4.3 kb (see GIBCO BRL Catalogue, page 318, 1992).

Therefore, Preston *et al.*,teach all limitations recited by claims 1-4, 6, 11, 12, 16, 19, 21, 25, and 26.

***Claim Rejections - 35 U.S.C. § 103***

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. Claims 5, 14, 15, 18, 23, 24, and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Preston *et al.*, (1994) as applied to claims 1-4, 6, 11, 12, 16, 19, 21, 25, and 26 above, and further in view of Samadpour *et al.*, (J. Clin. Microbiol. 31, 3179-3183, December 1993).

The teaching of Preston *et al.*, have been summarized previously, supra.

Preston *et al.*, do not disclose: (1) *Salmonella* isolates as described in claims 5 and 27; (2) using 5-30 μg of genomic DNA as described in claims 14 and 23; (3) agarose gel as described in claim 18; and (4) elimination of all DNA fragment less than 2 kb as described in claims 15 and 24.

Samadpour *et al.*, teach molecular epidemiology of *Escherichia coli* 0157: H7 strains by bacteriophage lambda restriction fragment length polymorphism analysis, which encompasses all

limitations recited by claims 5, 14, 18, 23, and 27. In this study, genomic DNAs prepared from 168 isolates of *Escherichia coli* O157:H7 were digested with four different restriction enzymes (EcoRI, HindIII, PstI, and PvuII), separated in 0.8% agarose gel (see page 3180, left column), and analyzed for restriction fragment length polymorphisms on Southern blots probed with bacteriophage lambda DNA. The isolates analyzed included strains from a recent large multistate outbreak of *E. coli* O157:H7 infection associated with consumption of poorly cooked beef in restaurants, a day-care center cluster, and temporally and geographically unrelated isolates. E. coli O157:H7 isolates recovered from the incriminated meat and from 61 of 63 patients (3/63 =4.8%) (considered as the lowest index of diversity from the unlinked panel) from Washington and Nevada possessed identical lambda restriction fragment length patterns. The lambda restriction fragment length polymorphisms observed in 11 of 12 day-care center patients were identical, but they differed from that of the strain associated with the multistate outbreak. E. coli O157:H7 from 42 patients temporally or geographically unrelated to either cluster of infection possessed 39 (40/42 =95.2%) unique and different lambda restriction fragment length patterns (considered as the highest index of diversity from the unlinked panel) (see abstract in page 3179 and left column in page 3182). Note that: (1) agarose gel used by Samadpour *et al.*, could separated fragment in the 0.1 to 18 kb range as described in claim 1 (see Figure 2 in page 3181) since the range of lambda markers digested by Hind III on the gel (see lane 1) were from 0.125 kb to 23.13 kb (see GIBCO BRL Catalogue, page 318, 1992); (2) although Samadpour *et al.*, did not show how much genomic DNA per each isolate was used for restriction digestion and how much genomic DNA per each isolate was loaded per lane in the gel as described claims 14 and 23, in the absence

of convincing evidence to the contrary the claimed invention, this limitations is considered as inherent to the reference taught by Samadpour *et al.*, since it is routine to one having ordinary skill in the art to digest 20-50 μg of genomic DNA and load 10 μg per lane for Southern Blot (see Nucleic Acid hybridization: a practical approach, edited by B D. Hames & S J. Higgins, 1985, pages 145 and 146); and (3) although Samadpour *et al.*, did not show to eliminate all DNA fragments less than 2 kb as described in claims 15 and 24, however, in the absence of an unexpected result, one having ordinary skill in the art at the time the invention was made could optimize experimental conditions to reach these goals since he or she could stop electrophoresis in any time.

Therefore, in the absence of an unexpected result, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have analyzed bacteriophage lambda RFLP in *Escherichia coli* O157 strains by agarose gel and Southern Blot hybridization because: (1) Southern Blot could provide another way to confirm the experimental results from RFLP analysis; (2) the simple substitution of one bacteria strain with known properties (*Shigella sonnei*) from another bacteria strain with known properties (*Escherichia coli* O157:H7), and the simple substitution of one well known gel separation (polyacrylamide gel) from another well known gel separation system (agarose gel) in RFLP analysis would have been, in the absence of an unexpected result, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made.

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their

expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

15. Claims 7, 9, 10, 17, and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Preston *et al.,* (1994) as applied to claims 1-4, 6, 11, 12, 16, 19, 21, 25, and 26 above, and further in view of Arakawa *et al.,* (J. Chromatography A, 664, 89-98, 1994).

The teaching of Preston *et al.,* have been summarized previously, supra.

Preston *et al.,* (1994) do not disclose to identify genetic subtypes among *Shigella sonnei* using capillary gel electrophoresis (3% polyacrylamide gel) as described in claims 7, 9, 10, 17, and 20.

Arakawa *et al.,* teach the detection of single base substitution in gene by capillary gel electrophoresis (see abstract in page 89). Note that Arakawa *et al.,* did not directly show to stain the gel with ethidium bromide as described in claims 10 and 20, however, in the absence of convincing evidence to the contrary, this limitations is considered to be inherent to the reference taught by Arakawa *et al.,* since it was routine to UV detect DNA fragments stained with ethidium bromide on a gel (see page 91, right column, first paragraph).

Therefore, in the absence of an unexpected result, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have identified genetic

subtypes among *Shigella sonnei* using capillary gel electrophoresis because the simple substitution of one well known gel separation system (regular polyacrylamide gel) from another well known gel separation system (capillary gel) in the separation of digested DNA fragments would have been, in the absence of an unexpected result, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made.

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

16. Claims 13 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Preston *et al.,* (1994) as applied to claims 1-4, 6, 11, 12, 16, 19, 21, 25, and 26 above, and further in view of Clayton *et al.,* (J. Clin. Microbiology, 31, 1420-1425, June, 1993) and Stratagene Catalogue (1994, page 211).

The teaching of Preston *et al.,* have been summarized previously, supra.

Preston *et al.,* (1994) do not disclose to analyze RFLP by double restriction digestion with two 6 base cutters as described in claim 13 or one 4 base cutter and one 6 base cutter as described in claim 22.

Clayton *et al.*, do teach to analyze RFLP by double restriction digestion with two 4 base cutters (see left column in page 1422, Figure 2 in page 1423, and Figure 3 in page 1424).

Stratagene Catalogue (1994) provides commercial available different restriction enzymes with 4 base and six base cutters (page 211).

Therefore, in the absence of an unexpected result, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have analyzed RFLP by double restriction digestion with two 6 base cutters or one 4 base cutter and one 6 base cutter because: (1) restriction enzyme with 4 and 6 cutters are commercially available; (2) the simple substitution of one or two commercial available restriction enzymes from another one or two commercial available restriction enzymes in RFLP analysis would have been, in the absence of an unexpected result, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

***Conclusion***

17. No Claim is allowed.

18. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is either (703) 308-4242 or (703)305-3014.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (703) 305-1270. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703) 308-1152.

Any inquiry of a general nature or relating to the status of this application should be directed to the Chemical Matrix receptionist whose telephone number is (703) 308-0196.

Frank Lu
June 15, 2001

Ethan Whisenant, Ph.D.
Primary Examiner (FSA)